Claim 74 **(previously added)** A pharmaceutical composition comprising the compound of claim 72.

REMARKS

After entry of the proposed amendment, claims 34, 40 and 45-74 will be pending in this application. Claims 75 and 76 have been canceled. Claim 70 has been amended to more clearly point out that the receptor is constitutively active. Claims 69 and 70 have been amended to recite "identifying said non-endogenous candidate compound as an inverse agonist or an agonist to said constitutively activated GPCR." No new matter has been added.

Applicants thank Examiner Basi for the indication that the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, have been withdrawn.

The Present Invention

The present invention involves Applicants' discovery that constitutively active orphan receptors can be successfully screened to obtain receptor modulators, without the need to know the endogenous ligand of the receptor. Prior to this discovery, the paradigm for drug discovery has been ligand-based assays, which measure the effect of a candidate compound on the binding or efficacy of a ligand at the receptor. This approach has necessarily involved knowledge of a ligand for the receptor under study.

Applicants discovered, *inter alia*, that it is more beneficial to determine activity of candidate compounds against the constitutively activated receptor – i.e., that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. See the present specification generally at pages 29-32. This novel approach has at least two benefits. First, because the method measures the effects of compounds on the activity of the receptor (as opposed to measuring the effect of compounds to antagonize the effect of the normal ligand), the present methods are more predictive of the efficacy of the compounds tested. Additionally, the present methods allow the direct identification of inverse agonists to the

receptor.

Rejections under 35 U.S.C. §112, second paragraph

Claims 34, 40, 45-70 and 75-76 are rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness in the recitation of various terms in the claims. Applicants respectfully traverse the rejection, as those of skill in the art would readily understand the present claims.

The Office Action asserts that the term "endogenous sequence" in claims 61 and 62, and the term "endogenous" in claims 69 and 70, are indefinite. The Office Action states that:

> The specification discloses the term endogenous means which is naturally produced by a mammal. It is not clear what parameter of the sequence determines if it is an endogenous sequence as compared with it not being an endogenous sequence. Further, since proteins can be mutated in nature as well as by the hand of man, it is not clear which sequences would considered endogenous and how they could be differentiated. Cells produce many proteins, all naturally, it is not clear which would be considered endogenous as compared to those that are not endogenous.

Office Action at page 3. The Office Action further asserts that claims 69 and 70 are indefinite on the basis that the metes and bounds of the term "endogenous " allegedly cannot be determined. However, Applicants respectfully assert that the Office has misinterpreted the terms "endogenous" and "non-endogenous", and that these terms are clear to those of skill in the art.

As acknowledged by the Office Action, the specification states that an "endogenous" material is one which a mammal naturally produces. Thus, "endogenous" refers to a material (for example a nucleic acid or protein) naturally produced by the genome of an organism. It is both implicit from the definition of "endogenous" provided in the specification, and explicitly understood by those of skill in the art, that an "endogenous" nucleic acid or protein is one that is produced by an organism ***in its natural state***; *i.e.*, a material produced by a cell, tissue or organ of an organism in the absence of any external genetic manipulation of the organism, including any material encoded by the genome of the organism (*See* the attached Declaration of Dr. Dominic Behan, hereinafter the "Behan Declaration", at paragraph 7). In addition, those of skill in the art, reading the present specification, would understand the term "non-endogenous" to refer to a material that is not produced by a cell, cell extracts, tissue or organ of an organism, for example a compound not produced by the organism

in its natural state, or a material produced as a result of external genetic manipulation (*See* Behan Declaration, at paragraph 7). Moreover, given the discussion above, it is apparent that those of skill in the art, reading the present specification, would have understood that the term "endogenous sequence," as used in the present claims, refers to a sequence of a particular protein or nucleic acid of interest, which is produced by an organism in its natural state or its cell extracts, tissues or organs. Thus, those of skill in the art, armed with the present specification, would easily understand what is meant by the terms "endogenous", "endogenous sequence" and "non-endogenous" in the context of the present claims. (*See* Behan Declaration, paragraphs 7 and 8).

The Office Action further asserts that claims 67 and 68 are indefinite for the recitation of "abnormal physiological function", apparently on the basis that the metes and bounds of that term cannot be determined. As best understood, the Office Action appears to assert that it is not possible to determine at what point a physiological function (for example sweating, motility of stomach and intestines, ureter function, salivary excretion, etc.) becomes "abnormal." Applicants respectfully disagree with the Office Action. For each physiological function recited in the Office Action there is an accepted normal range recognized by medical practitioners. Indeed, the entire field of medical diagnosis itself is largely directed to determining when such physiological functions are abnormal. Since those of skill in the art would be able to understand when such physiological functions are abnormal, those of skill in the art would understand what is being claimed. Accordingly, the questioned claim language is definite. See M.P.E.P §2173.05(b) ("Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is being claimed.").

To the extent that the Office Action intended to assert that the present specification must contain a specific recitation of the criteria for establishing the presence of each possible "abnormal physiological function", Applicants respectfully assert that it is not incumbent upon Applicants for a patent to provide such data. Rather, it is sufficient that those of skill in the art would recognize when a given physiological function is "abnormal". Significantly, the Office Action has provided no evidence that the art skilled are incapable of making such a determination. Accordingly, Applicants respectfully assert that the questioned term is definite within the patent laws.

The Office Action further asserts that claims 69, 70 and 75 are indefinite, apparently on the basis that the correlation of the receptor to physiological function is not clear. As best understood, the Office Action appears to question what aspect of receptor function defines the correlation to a physiological function. However, and again with respect, Applicants assert that those of skill in the art, reading the present specification, would know that the phrase used in the present claims, i.e., "... said receptor has been correlated with at least one mammalian physiological function...", refers to a receptor that has, for example, been shown to be expressed in a location that indicates its function. See for example Milligan, G., Biochemical Society Transactions 30 (4) 789-793 (2002) (a copy of which is provided herewith) in the paragraph bridging pages 789 and 790, which describes such correlation of location with function. Also see the Declaration of Michael E. Lewis, Ph.D., which was filed with Applicants' Response to Office Action mailed July 19, 2001. The Lewis Declaration makes it clear that those of skill in the art would have understood the correlation between receptor location and physiological function, and that such relationships were well known in the art prior to April 14, 1997 (the priority date of the present application). Accordingly, those of skill in the art would have understood what is meant by the phrase "... said receptor has been correlated with at least one mammalian physiological function..." as used in claims 69 and 70. Applicants further note that the Office Action has provided no evidence supporting its assertions. Thus, should this basis of rejection be maintained, Applicants request that the Office provide such evidence, including an appropriate affidavit under 37 C.F.R. 1.104(d)(2).

The Office Action further asserts that claims 69 and 70 are indefinite on the basis that the term "reporter signal" in unclear. While claims 69 and 70 have been amended to remove reference to the questioned language, thus rendering this aspect of the rejection moot, Applicants nevertheless respectfully assert that the term "reporter signal" is standard terminology in the art, and understood to mean the parameter (i.e., the "signal") measured in an assay system. In the context of claims 69 and 70, those of skill in the art would readily understand that such a reporter signal refers to the signal used in a given assay that is indicative of the function of the receptor. Such reporter systems are routine in the art, and several are disclosed in the present specification at, for example, pages 54 et seq.

The Office Action asserts that claim 76 is indefinite on the basis that it allegedly is not clear to which animal the compound is being administered. Specifically, the Office Action asserts that if an animal does not contain the GPCR under investigation, then administration of the compound to the animal will not result in an increase or decrease of physiological function. While claim 76 has been cancelled herein, thus rendering the rejection moot, Applicants nevertheless point out that claim 76 by its plain terms implies the presence of such a GPCR.

The Office Action further rejects claims 69 and 70 on the basis that it is allegedly unclear how the GPCR is subjected to constitutive activation. As a preliminary matter, Applicants respectfully point out that claim 70 recites an endogenous constitutively active GPCR (i.e., a GPCR that is constitutively active in its native state) and thus does not imply subjecting the GPCR to constitutive activation. Applicants have amended claim 70 herein to make this more clear. With regard to claim 69, Applicants respectfully point out that the present specification makes it clear that ***any*** method for achieving constitutive activation can be used. Inasmuch as the present specification provides an extensive discussion and nonlimiting examples of such methods at pages 35-57, it is not seen how those of skill in the art would fail to understand what is being claimed. Thus, should the rejection be maintained, Applicants respectfully request that the Office provide evidence of why those on skill in the art would fail to understand the language of the claims.

In view of the discussion presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

New Matter Rejection

Claims 75 and 76 are rejected under 35 U.S.C. § 112, first paragraph, for alleged new matter. While Applicants disagree with the rejection for reasons of record, solely for the purpose of advancing prosecution, Applicants have cancelled claims 75 an 76, thus rendering this rejection moot.

Rejection under 35 U.S.C. §112, first paragraph - Enablement

Claims 34, 40, 45-70 and 75-76 are rejected under 35 U.S.C. §112, first paragraph, for

alleged lack of enablement. Applicants respectfully traverse the rejection, as the claims are fully enabled under the patent laws.

The Office Action appears to assert that claims 70, 40, 53-60, 64, 66, 68 and 75 lack enablement on the basis that the specification provides an insufficient number of examples of constitutively active orphan GPCRs that have been correlated with a physiological function. The Office Action further asserts with respect to claims 34, 45-52, 63-65 and 67 that:

> ... there is no disclosure of GPCRs, with no known ligand, that are associated with a physiological function that can be constitutively activated to be used in the methods of the instant invention.

Applicants respectfully point out, however, that the mere number of examples contained in a patent specification is not determinative of enablement. See M.P.E.P. §2164.02 Indeed, it is established law that there is no requirement at all for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Rather, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

Thus, any assertion by the Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). In the present instance, the Office Action has not pointed to any evidence to support its assertions of non-enablement.

The present claims recite methods for directly identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous GPCR, wherein, *inter alia*:

-- location of expression of said receptor in a mammalian tissue source is known;

-- the receptor has been correlated with at least one mammalian physiological function; and

-- an endogenous ligand for the receptor has not been identified.

The Office Action appears to have based the present rejection largely on its view that a sufficient number of receptors meeting these criteria have not been disclosed. However, the relevant question is not whether the specification ***lists*** numerous such receptors, but rather whether the specification enables those of skill in the art to ***practice the invention of the claims without undue experimentation***. The Office Action has provided ***no evidence*** that those of skill in the art would be unable to determine the expression of a given receptor in a mammalian tissue. Indeed, such data in many instances is available in the literature, and such determinations are made by well established procedures in the art that are the epitome of what can be considered to be "routine". Likewise, the Office Action has provided no evidence that those of skill in the art would be unable to correlate the receptor with at least one mammalian physiological function, or determine whether a receptor is known to have an endogenous ligand. Each of these determinations are accomplished by experimentation that is routine, and well within the skill of those in the art, particularly when armed with the present specification. In the absence of evidence that the skilled artisan would be unable to make these determinations, the present rejection cannot stand.

The Office Action further states that there is no disclosure of:

> ... how to predictably create constitutively activated receptors with an associated physiological function that cause at least a 30% difference in receptor signal.

While claims 69 and 70 have been amended to remove reference to the "30% difference in reporter signal", Applicants nevertheless point out, as discussed above, that the present specification is replete with discussion of the methods for achieving constitutive activation (See the present specification at, for example, pages 35-52). Further, the Office Action has pointed to no evidence that such methods would fail to achieve constitutively activated receptors evidencing a 30% difference in reporter signal. Thus, it would appear that the Office Action has engaged in mere speculation in this regard, which is an improper basis to support a rejection for lack of enablement.

The Office Action provides on page 8 a discussion of constitutive activation of receptors, apparently for the purpose of supporting a conclusion that the claims lack enablement because they do not recite a specific method of constitutive activation. The Office Action appears to base its assertion on its own conclusion that "[t]here is no disclosure on how to constitutively activate receptors with no known ligand that have been associated with a physiological function." However, the Office Action has not provided any evidence or reasoning why such constitutive activation would be any different from constitutive activation of ***any*** orphan GPCR (or indeed any GPCR for which the endogenous ligand is known), regardless of whether it has been correlated with a physiological function. And, as stated above, the present specification provides a detailed discussion of such activation methods. To the extent that the Office Action seeks to require that Applicants provide proof that every possible GPCR can be constitutively activated by the methods disclosed in the specification, Applicants respectfully point out that the patent laws do not require Applicants to shoulder such a burden. Applicants have provided in their specification a detailed discussion of constitutive activation techniques that those of skill in the art are readily able to use. The ***possibility*** that there may be some GPCRs that will not display constitutive activation when subjected to one or more of these procedures simply is not a basis for maintaining a rejection for lack of enablement.

The Office Action further states on pages 8-9 that:

> There is no disclosure in the specification on the relationship of physiological function with other orphan receptor. Further, there is no indication that the

> constitutively activated receptor will have the same physiological function as the non activated receptor. Therefore ligands that bind one species (i.e. constitutively activated) may not have the same effect as those that bind the other species (i.e. non-constitutively activated). The specification does not disclose how to use the compounds that may be identified that have completely different effects on activated and non-activated receptors.

However, and with due respect, this is sheer speculation, totally unsupported by any evidence whatsoever. The Office Action has provided no evidence at all that a constitutively activated receptor will not have the same function, or binding properties, as the wild type receptor.[1] Indeed, the present specification states that constitutively activated receptors were shown to have increased affinity for normal agonists, without increased affinity for antagonists, which belies the assertion of the Office Action. As the precedent cited above makes abundantly clear, in the absence of evidence supporting its assertion, speculation such as that provided by the Office Action cannot form the basis of an enablement rejection.

The Office Action further asserts on page 9 that "Applicant has not disclosed how to use the compounds identified by the claimed method and do not have an effect on physiological function." Thus, it appears that the Office Action is speculating that identified compounds will fail to have an effect on a physiological function. However, and with respect, the present claims recite that any identified compound will be an agonist or inverse agonist of the receptor that has been correlated with at least one mammalian physiological function. Inasmuch as the Office Action has provided no evidence supporting its assertion that such agonists or inverse agonists will fail to have an effect on a mammalian physiological function, Applicants respectfully assert that this is another improper basis for the present rejection.

The Office Action concludes that those of skill would be unable to use the claimed invention because:

> ... The quantity of experimentation required would include identifying an orphan GPCR, associating a physiological function to the orphan receptor, determine if it is constitutively active, or make a constitutively active GPCR.

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1 Of course, for receptors that are constitutively active in their native state, this issue is simply irrelevant.

However, as discussed above, none of these steps imply undue experimentation. Identifying an orphan GPCR can be done by many routine methods in the art, including those as simple as merely referencing the literature. Associating the receptor with a physiological function by, for example, tissue expression studies or referencing the literature, also involves strictly routine techniques. Determining constitutive activity can be performed according to any of several routine assay techniques known in the art, and constitutive activation, as described in the specification, also can be accomplished by using known techniques. Accordingly, the present claims are fully enabled under the patent laws. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

Claims 34, 40, 45-70, 75 and 76 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description. Applicants respectfully traverse the rejection, as the claims are fully described by the present specification.

Specifically, the Office Action asserts that the present invention is not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventors had possession of the claimed invention. In support of its assertion, the Office Action states on page 10 that:

> No guidance is provided in the specification as to what minimal structural requirements are necessary for constitutive activation of GPCRs with no known ligand. There is a lack of representative number of species of GPCR with no known ligand and associated physiological function. There is a lack of guidance on how to modify different families of GPCR to be constitutively active. It does not appear that Applicants were in possession of the genus of orphan receptors with an associated physiological function to be used in the claimed method at the time the invention was made.

Thus, and as best understood, the Office Action appears to assert that the claims lack written description because the specification does not (1) provide guidance regarding constitutive activation of different classes of GPCRs; (2) list enough orphan receptors that are associated with a physiological function; (3) provide guidance regarding how to modify different families of

GPCR to be constitutively active; and (4) describe a "genus of orphan receptors with an associated physiological function."[2] However, as discussed above, the specification contains a detailed discussion of techniques for constitutive activation applicable to both orphan and non-orphan receptors. And the present specification describes (as the Office Action admits) one orphan receptor that has been correlated to a physiological function, as well as methods for ascertaining such correlation (See the specification at, for example, pages 33-35). Thus, it is not seen how the Office Action can fairly assert points (1) and (3) above.

In contravention to the apparent assertion of the Office Action implicit in points (2) and (4), the written description requirement does not require Applicants to list a "genus of orphan receptors with an associated physiological function." What is required is that the specification must ***reasonably*** convey to those of skill in the art that the inventors were in possession of the claimed invention. It simply is not necessary for Applicants to provide a "genus" of orphan receptors correlated with a physiological function in order to apprise the art skilled that they were in ***possession of the claimed methods***. Indeed, the Office Action has provided no reasoning at all why those of skill in the art would not understand Applicants to have invented the invention of the claims, given the disclosure in the specification of techniques for constitutive activation and methods for ascertaining such correlation. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §103(a)

Claims 70 and 76 are rejected under 35 U.S.C. 103(a) for alleged obviousness over U.S. Patent No. 6,087,115 to Gershengorn ("Gershengorn"), in view of U.S. Patent No. 6,093,806 to Cesarman et al., ("Cesarman"), and U.S. Patent No. 6,255,089 to Teitler et al. ("Teitler").

As discussed both above and in the present specification, Applicants discovered, *inter alia*, that constitutively active orphan receptors can be successfully screened to obtain receptor

2 While the Office Action cites Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1115 for the proposition that "the written description provision of 35 U.S.C. §112 is severable from its enablement provision," the Office Action appears to question the perceived lack of guidance "as to what minimal structural requirements are necessary for constitutive activation of GPCRs with no known ligand". Thus, this aspect of the rejection appears to be an allegation that those of skill would be unable to make and use the invention, i.e., a rejection under the enablement

modulators, without the need to know the endogenous ligand of the receptor. Prior to this discovery, the paradigm for drug discovery had been assays that required a known ligand for the receptor. The assay employed in the Gershengorn reference is an example of such a ligand-dependent assay.

> The Office Action asserts on pages 11-12 that it would have been obvious to:
>
> ... use the assay for identifying compounds to constitutively activated GPCR taught by Gershengorn to identify agonists and inverse agonists to constitutively activated GPCR of Karposi's virus taught by Cesarman, and vary the reporter signal measured to indicate differences of up to 30% between signal induced by compound and absence of compound as taught by and Teitler.

However, as pointed out above, claim 70 recites that an endogenous ligand for the receptor has not been identified. The Gershengorn reference states that its KSHV GPCR exhibits binding characteristic of a chemokine receptor, and identifies the rank order of binding of several such endogenous ligands. See Gershengorn at col. 8, lines 26-29. Thus, the Gershengorn reference does not disclose the assays of the present invention, which are performed on GPCRs for which an endogenous ligand has not been identified.

Further, Gershengorn reports that the binding characteristics of KSHV GPCR were determined using radiolabeled IL-8 and other chemokines ***in a competition analysis***. See Gershengorn at col. 8, lines 12-24. In contrast, the claimed methods recite that the candidate compound is ***directly identified***. As can be seen from the definitions of "directly identified" and "indirectly identified" on pages 18 and 19 of the specification, the Gershengorn assay would be an example of "indirectly identifying" a candidate compound. Significantly, the Gershengorn reference provides no suggestion whatsoever of "directly identifying" a candidate compound, as is required by the present claims.

Moreover, as the Office Action appears to recognize, the Cesarman reference merely describes the receptor identified in the Gershengorn reference, and does not provide any teaching of the present invention. The Teitler reference discloses two known serotonin receptors, which are by definition not orphan receptors as required by the present claims. Thus, the secondary

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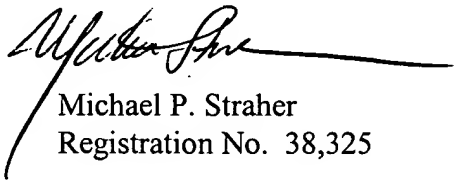
requirement of section 112, first paragraph, which Applicants have addressed above.

references fail to cure the deficiencies of the Gershengorn reference. Accordingly, the cited art, either alone or in combination, cannot be said to render the present claims obvious. Applicants therefore respectfully request withdrawal of this rejection under 35 U.S.C. §103(a).

Applicants respectfully submit that this application is in condition for allowance, and respectfully request early notification of the same.

Applicants invite the Examiner to contact the undersigned at (215) 665-5548 to clarify any unresolved issues raised by this amendment.

Respectfully submitted,



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